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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PERLEGEN SCIENCES, INC.
LEGAL DEPARTMENT
2021 STIERLIN COURT
MOUNTAIN VIEW, CA 94043

EXAMINER	
WHALEY, PABLO S	

ART UNIT	PAPER NUMBER
1631	

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10/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/768,788	BERNO, ANTHONY	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-16, 18-26,28-133 and 135-138, 140-141* is/are pending in the application.

4a) Of the above claim(s) *50,51,53,55-63,116 and 119-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-16,18-26,28-49,52,54,64-72, 75-109, 111-114,117-118,133,135-138,140 and 141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' remarks, filed 08/02/2007, have been fully considered. The following rejections and/or objections are maintained, newly applied, or withdrawn for the reasons set forth below. They constitute the complete set presently being applied to the instant application.

STATUS OF THE CLAIMS

Claims 1, 3-5, 7-16, 18-26, 28-49, 52, 54, 64-115, 117, 118, 133, and 135-141 are herein under examination. Claims 140 and 141 are newly added. Claims 2, 6, 17, 27, 134, and 139 are cancelled. This application contains claims 50, 51, 53, 55-63, 116 and 119-132 drawn to an invention nonelected with traverse in the response filed 03/24/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

CLAIM REJECTIONS WITHDRAWN

The rejection of claims 108-115 and 117 under 35 U.S.C. 101 because these claims were drawn to non-statutory subject matter is hereby withdrawn in view of applicant's amendments to the claims.

CLAIM REJECTIONS - 35 USC § 102

The rejection of claims 1, 4, 5, 7, 11-22, and 133 are rejected under 35 U.S.C. 102 (b) as being anticipated by Schork et al. (US 6,291,182; Issued Sept. 18, 2001) is hereby withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 7, 11-16, 18-22, 24, 91-97, 103-107, 133, 140, and 141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schork et al. (US 6,291,182; Issued Sept. 18, 2001), in view of Sham et al. (Nature Reviews Genetics, November 2002, Vol. 3, p.862-871).

This rejection is necessitated by amendment.

Claim 1 has been amended to recite new limitations directed to collecting first and

second pooled samples from case and control groups based on presence (and lack of presence) of phenotypic characteristics of interest, and determining relative allele frequencies from probe intensity signals. Applicant's arguments that Schork do not teach collecting first and second pooled samples from case and control groups have been considered but are moot in view of the new ground(s) of rejection.

As set forth in detail in the previous office action mailed 01/29/2007, Schork et al. teach methods, software, and apparatus for determining whether a genomic region harbors a gene with a detectable trait [Abstract]. More specifically, Schork et al. teach the following aspects of the instantly claimed invention:

- First group of between 50 and 300 "trait +" (i.e. case group) individuals recruited according to their phenotypes, and a second group of "trait -" individuals (i.e. control group) [Col. 21, lines 15-25] and [Fig. 7], as in claim 1.
- Calculation of differences in allele frequencies between trait + and trait – groups using biallelic markers to characterize interrogation positions associated with a phenotypic trait of interest [Col. 21, lines 25-67] and [Col. 22, lines 1-10], as in claims 1, 140, and 141.
- Association studies based on the determination of allele frequencies from case and control groups wherein polymorphism interrogation positions are associated with Alzheimer's' disease (AD) [Col. 50, Example 10], [Col. 52, lines 46-55], and output of results [Table 2], [Fig. 7], and [Ref. Claim 27], as in claims 1, 4, 5, 7, 11.
- 225 disease patients and 248 control patients, which are independent of each other [Col. 52, lines 46-55], as in claims 12, 13, 14.
- Candidate genomic regions (i.e. interrogation positions) comprising biallelic markers (i.e. SNPs) for individuals associated and not associated with detectable traits (i.e. phenotypic characteristics of interest) [Ref. Claim 1], as in claim 15 and 16.

- DNA samples labeled with fluorescein ddNTP markers [Col. 51, lines 55-65], as in claims 20 and 21.
- Pooling of genomic DNA samples, characterization of polymorphisms using sequence evaluation using software designed for detecting presence of biallelic sites (i.e. polymorphisms) among pooled fragments based on intensity ratios between peaks [Col. 46, Example 6], as in claims 17, 18, 19, 22.
- Microsequencing reactions performed using 5'-biotinylated oligonucleotide primers and fluorescein-dideoxynucleotides [See Example 13, Col. 56], as in claim 24, wherein the biotinylated oligonucleotide is annealed to the target nucleic acid sequence immediately adjacent to the polymorphic nucleotide position of interest.
- Comparing distributions using any method that is familiar to one of ordinary skill in the art (e.g. Wilcoxon rank test or the Kolmogorov-Smirnov test) using software that determines statistical difference between particular haplotypes found in control and trait-associated individuals [Col. 31], as well as pooling and ranking of samples [Col. 31, lines 30-60], which equates to claims 94-97.
- Association studies wherein interrogation positions of specific markers are validated by comparing allele frequencies of controls and patients Alzheimer's [Col. 52 and Table 2], as in claims 103-107.
- Apparatus and program storage device comprising instructions for implementing the above method steps [Col. 1, lines 49-60], [Ref. Claim 39], as in claim 133.

Schork et al. do not specifically teach collecting first and second pooled samples from case and control groups, as in claim 1, but do suggest association studies based on the

determination of allele frequencies from case and control groups wherein polymorphism interrogation positions are associated with Alzheimer's' disease (AD).

Sham et al. teach methods of DNA pooling as a practical way to reduce the cost of large-scale association studies to identify susceptibility loci for common diseases in quantitative genotyping assays [Abstract]. In particular, Sham teaches protocols for DNA pooling [Fig. 1], methods for determining allele frequencies in pooled samples [p.866, Col. 2] and [Fig. 2], and nucleic acid hybridizing probes [p.865, Box 1], as in claim 1. Sham also provides case-control studies of pooling efficiency with N cases and N controls [Box 2], as in claim 1. Sham also teach overcoming distorted relative allele measurement due to PCR phase using real-time detection methods that monitor amplification efficiency, as well as signal intensity, as the PCR progresses [p.865, Col. 2, ¶1], which is a teaching for measurement of intensity signals . Sham also teach that pooling beneficially allows allele frequencies in groups of individuals to be measured using fewer PCR reactions. For example, the allele frequencies in a sample of 500 cases and 500 controls can be measured from two pooled samples, rather than from 1,000 individual samples, which represents an increase in efficiency of 500-fold [p.862, Col. 1].

It would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to combine the known genomic analysis method taught by Schork et al. using the large-scale DNA pooling protocol taught by Sham et al., as DNA pooling is well known to have applications in mutation detection, association studies, and estimating disease prevalence in case-control studies, as suggested by Sham [p.862, Col. 1], resulting in the practice of the instantly claimed invention with predictable results. One of ordinary skill in the art would have been motivated to combine the above teachings in order to reduce the cost of large-scale association studies for identifying susceptibility loci for common diseases using far fewer PCR

reactions and genotyping assays, as set forth above by Sham. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

Claims 1, 3-5, 7, 10, 11, 15, 17-21, 24-25, 28-39, 40, 41-47, 48, 49, 52, 75, 76, 78, 108-115, 133, 135-138, 140, and 141 are rejected under 35 U.S.C. 103(a) as being made obvious by Fan et al. (Genome Research, 2000, Vol. 10, p.853-860), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kellam et al. (Antimicrobial Agents and Chemotherapy, 1994, Vol. 38, No. 1, p. 23-30), and further in view of Sham et al. (Nature Reviews Genetics, November 2002, Vol. 3, p.862-871).

This rejection is necessitated by amendment.

Applicant's arguments that Fan do not teach the above newly recited limitations directed to collecting first and second pooled samples from case and control groups, and determining relative allele frequencies from probe intensity signals have been considered but are moot in view of the new ground(s) of rejection.

As set forth in detail in the previous office action mailed 01/29/2007, Fan et al. teach a method for genotyping SNPs using generic high-density oligonucleotide arrays that contain thousands of 20-mer oligonucleotide tags [Abstract]. More specifically, Fan et al. teach the following aspects of the instant invention:

- Measurement and analysis of first, second, and third measurements of relative allele fractions (i.e. frequency) based on hybridization results from 44 individuals at two distinct SNP positions [Fig. 3 and Abstract], which is a teaching for the first and second measures as in instant claim 1.

- Genotyping of 44 individuals for 142 human SNPs previously identified in hypertension candidates (i.e. phenotypic characteristic of interest) [Abstract] using perfect match (PM) probe data and mismatch (MM) control probe data [p.853, Col. 2, ¶ 2], which correlates to human case and control groups as in instant claims 3, 4, 5, and 11.
- Cluster analysis of hybridization results of 44 individuals (i.e. 10-100,000) at two SNP markers [Fig. 3], as in instant claims 6 and 15.
- Allele frequency estimation for observed (i.e. unknown) versus known data based on SNPs at the interrogation position using a reference allele "C" [Fig. 5], as in instant claim 16.
- DNA data pooled in equal amounts from three groups [Fig. 5], as in instant claims 17-19.
- DNA label with detectable fluorescein and biotin-labeled markers attached to an array [Fig. 1], as in instant claims 20-21 and 24-25.
- Fluorescent intensity signals from > 32,000 probe pairs based on quantification of relative allele fraction values (i.e. relative allele frequency) [Fig. 2], as in instant claim 28.
- Over 64,000 20-mer probes each occupying an area of 30 μm^2 [p.853, Col. 2, ¶ 2], which meets the limitation of instant claims 29-31 and 32-34.
- Fluorescent intensities are measured and corrected via background subtraction [p.854, Col. 1, ¶ 1 and Fig. 2], as in instant claims 35-37, wherein background signals are inherently of the lowest intensity.
- Relative allele fraction values [Fig. 2(B)] and cluster analysis of hybridization results [Fig. 3], which are teachings for detection evaluation as in instant claim 39 and mismatch and perfectly complementary probes as in instant claim 40.

- Perfect match (PM) probes are paired with mismatch (MM) probes differing by a single base for hybridization-control [p.853, Col. 2, ¶ 2], which correlates to probes and reference probes with varying nucleotides as recited in instant claims 41, 42, and 47.
- Varying nucleotides at the interrogation position comprising A, C, and G [Table 1], as in instant claim 43.
- Observed versus known allele frequency estimation based on SNPs at the interrogation position using a reference allele "C" [Fig. 5], which is a teaching for the limitations of instant claim 48.
- Measurement of allele frequencies using PM and MM intensities (i.e. at least two intensity signals), as required by Specie B and recited in instant claims 52.
- Fluorescein and phycoerythrin hybridization signals (i.e. reference and alternate signals) [Fig. 2], as in instant claims 49, 50 and 52; relative allele fraction values (P) determined by calculating the log of total fluorescence intensity $(PM\text{-}M`M)_{fluorescein}$ / $[(PM\text{-}MM)_{fluorescein} + (PM\text{-}MM)_{phycoerythrin}]$ [Fig. 2], which correlates to instant claims 49-52, 108, 109, 140, and 141. It is noted that PM-MM intensity values are based on allele concentration [Fig. 4].
- A plurality of paired measurements [Fig. 3], as in claims 75, 76, and 78.
- Intensity data is corrected for background and spectral overlap [p.854, Col. 1, ¶ 1], as in instant claims 113 and 114.
- Exclusion of outliers from computed ranges of data sets [p.859, Col. 1, ¶ 1], as in instant claim 112.

The specification discloses that the "relative allele frequency" (P) for a SNP position indicates the proportion of the reference and alternate alleles at the SNP position, wherein P "could be calculated" from the concentration of the reference allele [00126]. However, this is not a limiting

definition for relative allele frequency. Fan et al. teach the measurement and analysis of first, second, and third measurements of relative allele fractions (i.e. frequency) based on hybridization results from 44 individuals at two distinct SNP positions [Fig. 3 and Abstract]. Therefore, the Examiner maintains that Fan et al. indeed teaches analyzing the relative allele frequencies in a computer system. Furthermore, Fan et al. teach the output of clustering analysis hybridization results of 44 individuals (i.e. 10-100,000) at two SNP markers [Fig. 3], indicative of individuals associated with hypertension.

Fan et al. do not specifically teach steps of collecting first and second pooled samples from case and control groups, as in claims 1, 133, and 138. However, Fan teaches method can also be used for allele-frequency estimation in pooled DNA samples, suggestive of case-control studies. Fan et al. also do not specifically teach a computer-implemented method for inputting allele frequency data into a computer system, as in instant claims 1 and 133-139, phenotypic characteristic of interest directed to resistance to a therapy, as in instant claim 10, calculating a background intensity equation as in claim 38, a plurality of measures, as in instant claim 75; arithmetic means as in claim 110, or correction equations as in claim 115.

Sham et al. teach protocols for DNA pooling [Fig. 1], methods for determining allele frequencies in pooled samples [p.866, Col. 2[and [Fig. 2], and case-control studies of DNA pooling with N cases and N controls [Box 2], as in claims 1, 133, and 138, and as set forth above. Sham also teaches the use of test statistics and significance values for determining allelic association [p.866, Col. 2] and [Fig. 2], as in claims 91-93, and averaging allele-frequency estimates in order to improve results [p.867, Col. 2].

Webster et al. teach computer-aided methods for analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions [0068] and monitoring gene expression [Abstract]. More specifically, Webster et al. teach the following aspects of the

instantly claimed invention: In a computer system: determining background subtraction and average intensities for probe data [0251], therefore the Examiner considers claims 38, 110, and 115 to be obvious variations of known equations for signal averaging as taught by Webster and invites the applicant to demonstrate the novel or unobvious difference between the claimed methods and those taught by Webster. anticipated as they are all directed to obvious forms of signal averaging; methods for determining the number of probes sets for reference tiling and alternate tilings based on fluorescent intensities (i.e. conformance values) [Fig. 8 and 9] and [0071], which equates to claims 44-46; inputting a plurality of hybridization intensities of pairs of perfect match and mismatch probes (i.e. first and second measures), as in instant claim 75, comparing (i.e. analyzing) the hybridization intensities of each pair of perfect match probes in order to generate a gene expression call of the sample nucleic acid sequence [Ref. Claim 13], which equates to steps of inputting and analyzing as in instant claim 1. Webster et al. further teach at least 2 intensity signal measurements for reference and alternate gene expression data [Fig. 8], as required by Specie B and recited in instant claims 52 and 108, and a computer system comprising a monitor, hard drive for storing and retrieving computer code for incorporating the invention, processor [0046] and [Fig. 2], and scanner [Fig. 3], as in instant claims 133-139.

Kellam et al. teach a rapid phenotypic assay for assessment of drug susceptibility of HIV isolates to reverse transcriptase inhibitors [Abstract]. More specifically, Kellam et al. teach the following aspects of the instantly claimed invention: phenotypic characteristic of interest is resistance to HIV treatment using therapeutic agent [Abstract, Tables 2 and 3], as recited in instant claim 10. It is noted that as Kellam et al. also provides a teaching for likelihood of resistance to infection, as in instant claim 7, as high resistance to a drug correlates to an increased likelihood for infection.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the method for genotyping SNPs taught by Fan et al. using the large-scale DNA pooling protocol taught by Sham et al., as DNA pooling is well known to have applications in mutation detection, association studies, and further using the rapid phenotypic assay for HIV taught by Kellam et al. in combination with a computer-implemented analysis method taught by Webster et al., resulting in the practice of the instant claimed invention with predictable results. One of ordinary skill in the art would have been motivated to combine the above teachings in order to reduce the cost of large-scale association studies using DNA pooling, taught by Sham, with a phenotypic assay better suited for complex resistance patterns in humans, as taught by Kellam et al. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and the rapid phenotypic assay taught by Kellam et al. with the method for genotyping SNPs taught by Fan et al. as Webster et al., Kellam et al., and Fan et al. all teach the genotypic and phenotypic analysis of data. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

Claims 69-74, 76, 77, 78, 80-82, 84, 85, 98, 99, 101, 102, and 118 rejected under 35 U.S.C. 103(a) as being unpatentable over Schork et al. (US 6,291,182; Issued Sept. 18, 2001), in view of Sham et al. (Nature Reviews Genetics, November 2002, Vol. 3, p.862-871), and further in view of Excoffier et al. (Mol. Biol. Evol., 1995, Vol. 12, No. 5, p.921-927).

This rejection is necessitated by amendment.

Schork et al. and Sham et al. make obvious methods, software, and an apparatus for determining whether a genomic region harbors a gene with a detectable trait using pooled

samples from case and control groups, as applied to claims 1, 4, 5, 7, 11-16, 18-22, 24, 91-97, 103-107, 133, 140, and 141 above. Additionally, Schork provides data indicative of association with a phenotypic trait (Alzheimer's) through interrogation positions, percentile differences in allele frequencies between disease and control groups, and corresponding p-values (i.e. thresholds) [Col. 53 and Table 2], which equates to the limitations of claims 100. As claims 101 and 102 are directed to the separation of data into top and bottom percentiles of calculated differences, which would be well within the capabilities of one of ordinary skill in the art, the Examiner considers these limitations to be obvious variations of known methods of data separation based on statistical significance and invites the applicant to demonstrate the novel or unobvious difference between the use of such methods and the teachings of the cited prior art.

Schork and Sham do not teach the limitations required by claims 69-74, 76, 77, 78, 80-82, 84, 85, 98, 99, and 118.

Excoffier et al. teach a computer-implemented maximum-likelihood estimation algorithm for determining molecular haplotype frequencies [Abstract]. More specifically, Excoffier et al. teach the following aspects of the instant invention: phenotype frequencies based on *m* phenotypes and listed in summation notation as in instant claims 69-71 [p.922, Col. 1, ¶ 3, and Equation (3)]; as claims 73 and 74 are based on corrective measures of allele frequency in summation notation format, the Examiner considers these limitations to be obvious variations of the known equations for determining frequency taught by Excoffier and invites the applicant to demonstrate the novel or unobvious difference the claimed equations and those taught by Excoffier. Also disclosed are methods for calculating a difference between first and second frequencies [p.924, Equation (10)], as in instant claims 72; iterative computation of successive haplotype frequencies [p.922, Col. 2, The EM Algorithm], as in instant claims 76, 84, and 99. As claim 85 is directed to specific threshold values and absolute differences between data, and as

Excoffier teaches difference calculations and the use of thresholds and a performance index for determining haplotype [p.924, Col. 1], claim 85 has not been given patentable weight over the teachings of Excoffier. Excoffier also teach polymorphisms simulated using four allele positions [p.923, Col. 2, ¶, 2], as in instant claim 77; pairing measures of estimated and actual allele frequencies [p.924, Col. 1, ¶ 2], as in instant claim 78; calculation of mean values of data [Table 1], as in instant claim 80; estimated frequencies based on threshold values that vary between 1 and 0 [p.924, Col. 1, ¶ 3], which equates to claims 81 and 82; generating estimated haplotype frequencies based on samples of 25 and 100 individuals and specific polymorphic positions [p.923, Col. 2, ¶ 2], as in claims 98; computer analysis of actual haplotype frequency measurements (i.e. first measure) compared to estimated haplotype frequencies (i.e. second measure) [p.924, Col. 1, ¶ 2], as in instant claim 118.

It would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to combine the known genomic analysis method using large-scale DNA pooling made obvious by Schork and Sham et al., with the maximum-likelihood frequency estimation algorithm taught by Excoffier et al., as Excoffier et al. [p.927, Col. 1, ¶ 1] suggest their algorithm could be successfully applied to microsatellite data and used to identify haplotypes formed by the combination of microsatellite patterns, resulting in the practice of the instantly claimed invention with predictable results. One of ordinary skill in the art would have been motivated to combine the above teachings in order to reduce the cost of large-scale association studies for identifying susceptibility loci for common diseases using a method that provides improvement over other estimation procedures, as taught by Excoffier [p.926, Col. 1]. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

Claims 1, 3, 4, 5, 48, 54, 75, 77, 79, 80, 81, 83, 84, 86-90, 98, 99, 100, 103, 104, 108, 109, 111, 112, 113, 135, and 136 remain rejected under 35 U.S.C. 103(a) as being made obvious by Germer et al. (Genome Research, 2000, Vol. 10, p.258-266), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6).

Applicant's again argue that Germer et al. do not teach determining relative allele frequencies in a case group and a control group. Applicant further argues that the combination of the above references fails to teach the step of measuring intensity signals from probes. Applicant's arguments have been fully considered but are not persuasive for the following reasons.

Germer et al. clearly teach the application of their method to association studies wherein allele frequencies are determined using case and control groups [p.256, Discussion], pooling of samples to measure allele frequency in order to provide considerable gains when doing case/control studies for detection of associations between genes and disease [p.264, Col, 1, ¶2], and association studies 1000 case and 1000 control samples using 10,000 SNPs [p.263, Col. 2]. Furthermore, Fig. 1 illustrates the basis of allele frequency measurement using PCR, wherein pooled DNA samples are divided into groups based on primer specificity (i.e. case and control) to SNP variation [Fig. 1]. Therefore, the Examiner maintains that Germer indeed teaches case/control studies and methods for measuring relative allele frequency based on fluorescence obtained from probes.

Webster et al. was not relied upon for the above limitations, but to provide evidence of a computer-aided method for: inputting a plurality of hybridization intensities of pairs of perfect match and mismatch probes (i.e. first and second measures), comparing (i.e. analyzing) the

hybridization intensities of each pair of perfect match probes [Ref. Claim 13] based on difference and ratio thresholds [Ref. Claims 14 and 15], as in instant claims 1, 75, and 80, 81, and 84. Webster et al. further teach mean hybridization intensities of photon counts recorded from a cell (i.e. at least two intensity counts [0099], as required by Specie B and recited in instant claim 52; background subtraction and thresholding of intensity data [Fig. 11], as in instant claim 100, and reference and alternate gene expression data [Fig. 8], as in instant claim 108.

Kroll et al. was not relied upon for the above limitations, but to provide evidence of a method for comparing measurements from gene expression data comprising normalization, mean, trimmed mean (i.e. outlier exclusion), and standard deviation [Abstract, Table 1, Table 2], as required by Specie C and recited in instant claims 54, 108, 111, and 112.

For the above reasons, and for those set forth in the detail in the office action mailed 01/29/2007, the Examiner maintains that it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the "trimmed mean" method of Kroll el al. and the computer-implemented method of Webster et al. with the high-throughput method for determining the allele frequencies of case and control data as taught by Germer et al. [p.256, Discussion], where the motivation would have been to use a more robust method for normalizing and comparing large data sets, as taught by Kroll et al. [Abstract] and in association studies [Germer et al., p.256, Discussion], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and using the trimmed mean method of Kroll et al. with the high-throughput method for determining the allele frequency of Germer et al. as all teach the analysis of gene expression data. Therefore, the instant claims do not recite any new element or new function or unpredictable result.

Claims 1, 3, 4, 5, 11, 12, 13, 17-19, 22, 23, 26, 28, 52, 64-68, 72, 75-77, 133, 135-138 are rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6) and further in view of Xiong et al. (Am. J. Hum. Genet., 1999, Vol. 64, p.629-640).

Applicant's arguments that Barcellos do not teach the above newly recited limitations directed to collecting first and second pooled samples from case and control groups, and determining relative allele frequencies from probe intensity signals have been considered but are not persuasive for the following reasons.

As set forth in the previous office action, Barcellos et al. specifically teach DNA samples obtained from human patient samples (n=51) and control individuals (n=75) [p.735, Methods and Materials], which is a teaching for first and second samples as in instant claims 1, 3, 4, 5, and 12; Pooling of patient and control DNA data and conversion to 2N allele-frequency counts for each pool size [p.736, Col. 2, ¶ 2] and labeling of samples with detectable marker as in instant claims 17-19; Use of pooled DNA amplification [Abstract], as in instant claim 22; and peak height data (i.e. signal intensity) from genotyping profiles using a dinucleotide marker (i.e. a first probe on a two-nucleotide array) [Table 1]. Furthermore, Barcellos clearly allele frequencies for pooled samples using peak heights derived from electropherograms [p.736, Col. 1, ¶2], which are well known to be based on fluorescence intensity of labeled probes (See: www.answers.com: An **electropherogram** is a plot of fluorescence units over time). Furthermore, DNA amplifications are quantitated using fluorescent assays for measuring fluorescent probe labels in samples [p.736, Col. 1, ¶2]. Therefore, the Examiner maintains that

Barcellos indeed teaches case/control studies and methods for measuring relative allele frequency based on fluorescence obtained from probes.

Webster et al. was not relied upon for the above limitations, but to provide evidence of a computer-aided method for inputting and analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions [0068] and monitoring gene expression [Abstract], as applied to claims 1, 52 (Specie B) 100, 108, and 133-139 above. Furthermore, Webster et al. teach the following aspects of the instantly claimed invention: allele frequency intensity blocks comprising a multitude of intensity patterns (i.e. further first and further second measures) at different interrogation positions [0071] [Fig. 7 and 8], as in instant claims 68, 75, 76, and 77.

Kroll et al. was not relied upon for the above limitations, but to provide evidence of a method for comparing measurements from gene expression data comprising normalization, mean, trimmed mean (i.e. outlier exclusion), and standard deviation [Abstract, Table 1, Table 2], as required by Specie C and as in instant claims 54, 108, 111, and 112.

Xiong et al. was not relied upon for the above limitations, but to provide evidence of a method for mapping genes involved in genetic diseases based on allele-frequency distribution differences between patient and control populations [Abstract]. More specifically, Xiong et al. teach the characterization of a disease locus containing biallelic polymorphisms using biallelic markers and calculation of biallelic marker frequencies [p.630, Col. 2, ¶ 2 and 3]. Xiong et al. also compare techniques using microsatellite markers and biallelic markers [Abstract].

For the above reasons, and for those set forth in the detail in the office action mailed 01/29/2007, the Examiner maintains that it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the computer-implemented analysis method of Webster et al., the trimmed mean technique of Kroll et al., and the use of biallelic markers taught by Xiong et al. with high-resolution genome screening of case/control data as

taught by Barcellos et al., where the motivation would have been to use a high throughput computer-implemented method for genotypic and phenotypic analysis of disease [Webster et al.] resulting in the practice of the instant claimed invention. Further motivation for using biallelic markers to characterize interrogation positions is provided by Xiong et al., who teach that biallelic markers are ideal for population-based mapping [p.630, Col. 1, ¶ 3]. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and the high-resolution genome screening method of Barcellos et al. as both teach method of genomic analysis using allele frequency intensity data sets. One of skill in the art would have had a reasonable expectation of successfully using the trimmed means technique of Kroll et al. and the high-resolution genome screening method of Barcellos et al. as Barcellos et al. teach exclusion of data [Table 4] and statistical analysis of data.

Claims 78-83 are rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997), Kroll et al. (2002), and Xiong et al. (1999), as applied to claims 1, 3, 4, 5, 11, 12, 13, 17-19, 22, 23, 26, 28, 52, 64-68, 72, 75-77, 133, 135-138, above, in further view of MathWorld (http://mathworld.wolfram.com/Pairedt-Test.html, © 1999 CRC Press LLC, p. 1-2) and The 2002 County Loan Rate Calculation Procedure (2002, p.1).

Applicants again argue that Barcellos do not teach the above newly recited limitations directed to collecting first and second pooled samples from case and control groups, and determining relative allele frequencies from probe intensity signals have been considered but are not persuasive for the following reasons.

The Examiner again maintains that Barcellos indeed teaches case/control studies and methods for measuring relative allele frequency based on fluorescence obtained from probes, as set forth above, as no additional arguments have been presented. Therefore, for the reasons set for above and in the office action mailed 01/29/2007, the Examiner also maintains that it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the computer-implemented method of Barcellos et al., Webster et al., Kroll et al. , and Xiong et al. with the data analysis methods as taught by MathWorld and The 2002 County Loan Rate Calculation Procedure, where the motivation would have been to remove outliers from the data set to improve the degree of closeness between allele-frequency distributions [Barcellos et al., p.737, Col. 1, ¶ 3]. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method made obvious by Barcellos et al., Webster et al., Kroll et al., and Xiong et al. with the Olympic Average and paired t-test as all teach the statistical analysis of data.

CONCLUSION

No claims are allowed.

Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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